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# Sleep and depression

## Theory and practice

### Background

Sleep disorders are particularly common in the primary care setting, and are intimately interlinked with depression.

### Objective

This article aims to review the relationship between sleep and depression, with an emphasis on the foundation and clinical salience of this relationship.

### Discussion

Depression is the most common cause of insomnia, and insomnia is highly prevalent in depression. This association has a well characterised physiological foundation. Sleep disorder in depression has prognostic and therapeutic implications. Residual insomnia after remission of depression is predictive of relapse, and prominent insomnia predicts a poorer treatment outcome in depression. Evidence based management involves integrating both pharmacological and behavioural strategies; the latter includes sleep hygiene and regulating diurnal rhythms.

■ **Insomnia is one of the most common presenting symptoms in the primary care setting, and depression is one of the most common causes of insomnia. Insomnia is a symptom not a diagnosis, and has a wide differential diagnosis that includes psychiatric disorders such as depression and anxiety, and pain, medical conditions and psychological causes. Conditioned, or psychophysiological insomnia, is a common form of insomnia, and occurs when anxiety that centres on not sleeping well generates arousal at bed time.<sup>1</sup> This anxiety about sleep sustains a cycle that perpetuates the insomnia. The aetiological foundations of insomnia, both psychological and biological, need to be the focus of management, rather than the symptom itself.**

Epidemiological data suggests that people with psychiatric disorders account for 30–40% of those in the community reporting symptoms of insomnia, and that depression is the most common psychiatric cause of insomnia. In individuals with insomnia, 40–60% have features of depression.<sup>2</sup> Sleep disorder is among the most prevalent symptoms of depression, with rates of around 80%.<sup>2</sup> A history of persistent insomnia is associated with a significantly increased risk of developing a new episode of depression.<sup>2</sup> Insomnia is also one of the most common prodromal features of depression. Sleep symptoms precede an episode of depression in 40% of cases.<sup>2</sup>

Sleep symptoms have clinically meaningful prognostic significance. Those people with depression who have prominent insomnia are likely to have a poorer response to treatment. Sleep disturbance is also predictive of a greater risk of suicidal behaviour.<sup>3</sup> Following response to treatment, persistent sleep disturbance robustly predicts a recurrence of new episodes of illness.<sup>4</sup>

The intimate nexus between sleep and depressive symptoms suggests a critical role for addressing sleep mechanisms in depression, and equally suggests that dysregulation of sleep may be a meaningful clinical marker.<sup>5</sup>



## The physiological foundation of sleep

Almost all animals, including humans, have a distinct circadian rhythm which sets multiple biological and behavioural processes. This rhythm is generated and maintained endogenously. The suprachiasmatic nucleus (SCN) in the hypothalamus is the central timekeeper. This endogenous clock adapts to, and is set by, a number of exogenous stimuli, of which light is the principal. Many physiological processes have a diurnal pattern and are governed by the 24 hour clock, including body temperature, endocrine and autonomic functions, sleep, cognitive processes and alertness. The diurnal pattern has a key role in assisting an organism to adapt to environmental circumstances. Many core psychological functions in healthy individuals such as mood, alertness and cognitive performances follow a diurnal pattern, being best in the morning and declining throughout the course of the day to an evening nadir.<sup>6</sup> There is similarly a diurnal pattern to the stress response, which may be of particular relevance to stress related disorders such as depression.<sup>7</sup>

The circadian clock has a genetic foundation. A range of genes, including the so-called 'clock' genes, regulate the length of the circadian period. Variants of this gene determine a person's diurnal preference, ie. being a 'night owl' or a 'morning lark', and these genes are further implicated in the pathophysiology of mood disorders. Lithium, which prevents relapse in both unipolar and bipolar disorder, affects the expression of the clock genes.<sup>8</sup>

The circadian patterns of hormones, including melatonin and cortisol, may be dysregulated in depression. These hormones play a core role in the regulation of many physiological processes. Melatonin is secreted nocturnally by the pineal gland, and its release has been used as a marker (zeitgeber) of circadian phase. About 2 hours before bed time there is a spurt of endogenous release of melatonin in response to dim light conditions. In depression, there is a pattern of delayed melatonin release, suggesting a phase delay in circadian rhythms. Patients who are suffering from depression may also be supersensitive to light induced suppression of melatonin. Lower levels of melatonin in depression is a consistent finding in both depression and bipolar disorder, and in both disorders, there is a tendency for the circadian cycle to phase advance, with delayed sleep and waking times.<sup>9</sup>

As many as 40–60% of patients suffering from depression have disturbances in the hypothalamic-pituitary-adrenal (HPA) axis, which manifest as changes in patterns of diurnal cortisol release. This can be measured by both the dexamethasone suppression test and the corticotrophin releasing hormone (CRH) stimulation test. Bright light therapy, which is an effective treatment for some patients, activates the SCN, inhibiting CRH release and suppressing HPA activity. Antidepressants may act by reducing HPA activity.<sup>9</sup> Putative antidepressants that act solely on the CRH system are being developed.

## Symptoms of depression and rhythms of sleep

The symptoms of depression characteristically vary with time of day. They tend to be more severe in the morning, improving throughout

the day. This diurnal shift in mood is particularly common in the melancholic patterns of depression, and is predictive of response to somatic treatment of depression. In depression, the normal pattern of circadian shifts in physiological functions such as temperature and hormonal patterns are altered, as are the diurnal patterns of change in noradrenaline and cortisone.

There is usually a cyclical shift in the pattern of arousal over the 24 hour cycle, where people suffering from depression tend to have heightened arousal across the day. This may be mediated by increased activity in those parts of the brain stem and hypothalamus that have a role in the maintenance of wakefulness.<sup>5</sup>

Typical sleep symptoms in depression include:

- difficulty initiating sleep (initial insomnia)
- difficulty maintaining sleep (mid insomnia), and
- early morning waking (terminal insomnia).

Hypersomnia is a pattern that is part of the 'signature' of bipolar depression.<sup>10</sup>

Changes to sleep architecture in depression include:

- shortening of the interval between sleep initiation and the first period of rapid eye movement (REM) sleep – known as REM latency, a well replicated biological marker of depression
- longer REM sleep, and
- a reduction in the amount of delta, or slow wave sleep.

## Treatment implications

The ability of older antidepressants to suppress REM sleep was so striking that it was initially hypothesised that this ability was a mechanism of action of antidepressants. That some newer antidepressants, including moclobemide, nefazadone and bupropion, have proven antidepressant efficacy and may actually enhance REM sleep, has however scotched that theory. The melatonin MT1 and MT2 agonist and 5HT2C antagonist agomelatine, increases slow wave sleep and normalises REM sleep in depression.<sup>11</sup>

The centrality of circadian rhythms in mood disorders has led to the development of specific psychosocial interventions that aim to normalise circadian rhythms. It is thought that there is a link between disruption of social rhythms and disruptions of physiological rhythms, and this may contribute toward vulnerability to depression. Social rhythms are modulated by environmental stimuli or social zeitgebers. These include social interaction, meals and other routines that share the capacity to modulate the circadian clock. Depression has the capacity to disrupt occupational and social routines, which might further increase vulnerability to mood symptoms. Life events including the birth of children, jet lag, and shift work, share an ability to disrupt rhythms and are often triggers of episodes of illness.

Frank et al<sup>12</sup> have modified interpersonal therapy, developed for the treatment of depression, to increase the focus on circadian rhythms, and developed interpersonal and social rhythm therapy. While developed predominantly in the context of bipolar disorder, it is applicable to circadian disruption in depression.<sup>13</sup> It involves the identification of the disrupted or irregular rhythms. This is done



Table 1. Behavioural tips for improving sleep quality

- Reduce stimulation such as noise or lights
- People sleep better in a cooler environment. Keep the room cooler rather than warmer
- Avoid stimulating activities, such as work or heated discussions before going to sleep
- Avoid caffeine (ie. coffee, cola drinks, chocolate) within 8 hours of bed time. Although many people think that caffeine doesn't affect their sleep, it does
- Avoid alcohol within 6 hours before bed time; it can reduce the quality of sleep
- Avoid smoking at least 2 hours before bed time; nicotine is stimulating
- Day time sleep adds to your 24 hour sleep cycle; avoid naps
- A regular exercise program helps sleep, but not if done just before bed time
- Put the bedside clock out of view to avoid 'clock watching' at night
- A light snack at bed time can be helpful
- Routine is critical. Getting up around the same time each day helps set your day/night clock; a consistent waking time is more important than bed time
- A 'wind down' routine before going to bed can help relax and make it easier to sleep. This can include activities such as reading, having a warm bath or listening to music
- Relaxation exercises, such as progressive muscle relaxation and breathing techniques, can reduce anxiety and assist sleep. This is particularly useful for conditioned insomnia, ie. insomnia generated by excessive worry about not sleeping
- If after some time sleep does not come, get up, go into another room and do a relaxing, quiet and soothing activity such as listening to soothing music, then return to bed

using a validated instrument, the social rhythm metric. Using the information obtained, targeted steps can be taken to normalise the disruption in rhythms, including establishing a regular sleep and wake time. As the dominant factor in entraining diurnal rhythms is light, the time one wakes up is one of the major factors that entrains such rhythms. Treatment involves establishing regular waking, sleeping and meal times, and trying as far as is practical to have a routine work and exercise pattern. The program needs to be personalised to the individual's life circumstances.<sup>14</sup>

Sleep hygiene principles that are simple to communicate and that assist in the regulation and nonpharmacological management of sleep complaints are detailed in *Table 1*. The principles of sleep hygiene centre on reinforcing of the sleep-wake cycle, and reducing factors that can disrupt this cycle.

## Conclusion

Insomnia is a common clinical issue, and depression one of the most common causes of insomnia. Sleep disorders contribute substantially to the community burden of disability, and is additive to the impact of depression.<sup>15</sup> Sleep and depression interact in a complex manner, and

while insomnia increases the vulnerability to depression, depression is frequently associated with altered circadian and social rhythms. Insomnia has prognostic significance in depression, and therapeutic strategies that target disruptions in circadian rhythm assist in the management of mood disorders.

## Summary of important points

- Insomnia is common in primary care, and depression is its most common cause.
- The relationship between insomnia and depression has prognostic and treatment implications.
- The physiological foundation of both sleep and insomnia is intimately interlinked.
- Behavioural treatments that regulate the diurnal rhythm are of proven efficacy in mood disorders.

Conflict of interest: grant/research support has been provided to the author by: Stanley Medical Research Foundation, MBF, NHMRC, beyondblue, Geelong Medical Research Foundation, Bristol Myers Squibb, Eli Lilly, Glaxo SmithKline, Organon, Novartis, Mayne Pharma, Servier Consultant/Speaker: Astra Zeneca, Bristol Myers Squibb, Eli Lilly, Glaxo SmithKline, Janssen Cilag, Lundbeck, Pfizer, Sanofi Synthelabo, Servier, Solvay, Wyeth.

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